IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT application of:		
	DUNCKLEY, *et al.*	) Conf. No.: 8410
		)
Serial No:	10/524,724	) Art Unit: 1635
		)
Filed:	February 16, 2005	) Examiner: Zara, Jane J.
		)
Title:	Modified Tailed Oligonucleotides	) Docket No: E072 1050.1

AMENDMENT & REPLY TO FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam/Sir :

This submission is responsive to the Final Office Action mailed July 23, 2009.

Also submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114.

Applicants assert that Applicants are a small entity and that small entity status is entitled to be asserted for the present application.

The Commissioner is authorized hereby to charge Deposit Account No. **09-0528** in the amount of: $405.00 covering the fee set forth in 1.17(e) for the RCE; and $555.00 covering the fee set forth in 1.17(a)(3) for an extension for reply through January 25, 2010 (January 23rd being a Saturday).

No other fees are believed to be due. Nonetheless, the Commissioner is authorized hereby to charge Deposit Account No. **09-0528** for any appropriate fees that may be due in connection with this submission.

Amendment to the claims begins on page 2 of this paper.

Remarks regarding this submission begin on page 8 of this paper.

Conclusion begins on page 19 of this paper.

Amendment to the claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1-22. (Cancelled).

23. (currently amended) A method of recruiting an RNA splicing factor to a target RNA species, the method comprising:

providing a nucleic acid molecule having a first nucleotide sequence ~~domain~~ capable of forming a first specific binding pair with a target sequence on the target RNA species by complementary base pairing, and a second nucleotide sequence ~~domain~~ capable of forming a second specific binding pair with an RNA splicing factor selected from the group consisting of SR proteins, SR-related proteins, hnRNP proteins, and U1 snRNP, wherein said second nucleotide sequence is not complementary to the target RNA species, and

contacting the nucleic acid molecule with the target RNA species and with the RNA splicing factor whereby the first specific binding pair and the second specific binding pair form to recruit the RNA splicing factor to an RNA splicing site on the target RNA species to effect RNA splicing of the target RNA at said RNA splicing site of the target RNA, wherein exogenous nucleic acid is not incorporated into the target RNA species.

24-27. (Cancelled)

28. (previously presented) A method according to claim 23 wherein the target sequence is within 100 nucleotides of an RNA splicing site on the RNA target species.

29. (Cancelled)

30. (currently amended) A method according to claim 23 for increasing the level of splicing at a specific splice site on a target RNA species, wherein the first nucleotide sequence ~~domain~~ of

the nucleic acid molecule forms a specific binding pair with a target sequence close to the specific splice site on the RNA species.

31. (previously presented) A method according to claim 30 wherein the specific splice site is a cryptic splice site or a mutated splice site.

32. (currently amended) A method according to claim 23 for increasing the level of incorporation of a specific exon in a pre-mRNA species into a mature mRNA species, wherein the first nucleotide sequence ~~domain~~ of the nucleic acid molecule forms a specific binding pair with a target sequence in a pre-mRNA species.

33. Cancelled

34. (previously presented) A method according to Claim 23 which is performed in an *in vitro* cell-free system.

35. (previously presented) A method according to Claim 23 which is performed in an *ex vivo* cellular system.

36. (previously presented) A method according to Claim 23 which is performed in an *ex vivo* tissue-based system.

37. (previously presented) A method according to Claim 23 which is performed *in vivo* in the human or animal body.

38. (currently amended) A method according to claim 23 of treating a condition characterised by defective or undesirable RNA splicing in an individual, the method comprising administering to the individual a nucleic acid molecule as defined in claim 23 wherein the first nucleotide sequence ~~domain~~ is capable of forming a specific binding pair with a target region of a defectively spliced target RNA species, and wherein the target region of the target RNA species

is sufficiently close on the RNA species to the site of defective or undesirable splicing for splicing at the site to be enhanced by the action of the splicing factor.

39-40. (Cancelled)

41. (previously presented) A method according to claim 38 wherein the defective RNA splicing is caused by a mutation at the site of defective splicing.

42. (previously presented) A method according to claim 38 wherein enhanced exonic incorporation is desirable at the site of undesirable RNA splicing.

43. (previously presented) A method according to claim 38 wherein the condition is selected from spinal muscular atrophy, breast cancer, Becker muscular dystrophy and β-thalassaemia.

44-60. (Cancelled)

61. (previously presented) A method according to claim 23, wherein the nucleic acid molecule is from 13 to 100 nucleotides in length.

62-65. (Cancelled)

66. (previously presented) A method according to claim 23, wherein said nucleic acid molecule comprises at least one modified nucleotide.

67. (previously presented) A method according to claim 66, wherein said at least one modified nucleotide is chemically modified to enhance stability or uptake by a cell.

68. (previously presented) A method according to claim 66, wherein said at least one modified nucleotide is selected from the group consisting of a 2'-*O*-methyl derivative of RNA, a

phosphorothioate modification, a morpholino modification and a phosphoroamidate modification.

69. (currently amended) A method according to claim 23, wherein said second nucleotide sequence ~~domain~~ comprises the sequence CAGGUAAGU.

70. (currently amended) A method according to claim 23, wherein said second nucleotide sequence ~~domain~~ comprises the sequence AGGAGGACGGAGGACGGAGGACA.

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71. (previously presented) The method of claim 23, wherein the nucleic acid molecule is expressed from a polynucleotide encoding the nucleic acid molecule.

72. (previously presented) The method of claim 71, wherein a vector comprises the polynucleotide.

73. (previously presented) The method of claim 72, wherein the vector is a plasmid.

74. (previously presented) The method of claim 72, wherein the vector is an inducible mammalian expression vector.

75. (previously presented) The method of claim 23, wherein a delivery system comprises the nucleic acid molecule, wherein the delivery system is selected from the group consisting of: a liposome, a virosome, a microsphere, and a microcapsule.

76. (previously presented) The method of claim 23, wherein a delivery system comprises the nucleic acid molecule, wherein the delivery system comprises a retrovirus or an adenovirus.

77. (currently amended) The method of claim ~~23~~ 43, wherein the condition is spinal muscular atrophy (SMA).

78. (Cancelled)

79. (New) The method of claim 69, wherein the target RNA species is an SM1 or an SM2 RNA.

80. (New) The method of claim 70, wherein the target RNA species is an SM1 or an SM2 RNA.

81. (New) A method according to claim 38, wherein said second nucleotide sequence comprises the sequence CAGGUAAGU.

82. (New) A method according to claim 38, wherein said second nucleotide sequence comprises the sequence AGGAGGACGGAGGACGGAGGACA.

83. (New) The method of claim 23, wherein the nucleic acid molecule comprises the sequence shown by SEQ ID NO: 10.

84. (New) The method of claim 38, wherein the nucleic acid molecule comprises the sequence shown by SEQ ID NO: 10.

85. (New) The method of claim 43, wherein the nucleic acid molecule comprises the sequence shown by SEQ ID NO: 10.

86. (New) The method of claim 23, wherein the RNA splicing factor is SF2/ASF.

87. (New) The method of claim 38, wherein the RNA splicing factor is SF2/ASF.

88. (New) The method of claim 43, wherein the RNA splicing factor is SF2/ASF.

89. (New) A method according to claim 69, wherein the step of contacting occurs in an *in vitro* cell-free system or an *ex vivo* cellular system.

90. (New) A method according to claim 70, wherein the step of contacting occurs in an *in vitro* cell-free system or an *ex vivo* cellular system.

REMARKS

Claims 23, 26, 28, 30-38, 40-43, and 61-78 are pending.

Claims 23, 30, 32, 38, 69, 70, and 77 are amended herein.

Claims 26, 33, 40, 62, 63, 64, 65, and 78 are cancelled.

Claims 79-90 are newly presented.

Support for the present amendment is found in the specification as originally filed. No new matter is introduced.

Applicants reserve the right to reintroduce cancelled subject matter, for example, in a later-filed continuing application.

Rejection of Claims under 35 U.S.C. §112, 1st paragraph (Written Description) is Traversed or Rendered Moot

The Office rejected claims 23, 26, 28, 30-38, 40-43, and 61-78 as allegedly failing to comply with the written description requirement. Office Action at page 2, lines 15-17; page 3, lines 6-17; page 4, lines 13-19; and page 8, lines 3-5. Of these claims, only claims 23, 28, 30-32, 34-38, 41-43, 61, and 66-77 remain pending. In view of the foregoing amendment and the following remarks, the rejection is traversed or rendered moot.

The Office maintains that:

> The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus of compounds claimed, and which provide for the functions claimed, which functions include recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual.

Office Action at page 4, lines 15-19. Thus, it appears that the Office maintains the rejection based on the Office's position that the claimed *method* amounts to an insufficient written description because the recited *nucleic acid molecule* is not adequately described.

In assessing whether the written description requirement is satisfied, "[t]he primary consideration is *factual* and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (citation omitted, emphasis in original). The amount of description needed to meet the requirement can vary with the scientific and technologic knowledge already in

existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). Morever, the Federal Circuit also has noted that "Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003).

Firstly, while Applicants do not concede the merits of this rejection, in order to advance prosecution, claim 23 (the only independent claim) is amended herein to include the recitation "*nucleic acid molecule having a first nucleotide sequence capable of forming a first specific binding pair with a target sequence on the target RNA species by complementary base pairing, and a second nucleotide sequence capable of forming a second specific binding pair with an RNA splicing factor selected from the group consisting of SR proteins, SR-related proteins, hnRNP proteins, and U1 snRNP, wherein said second nucleotide sequence is not complementary to the target RNA species.*"

As noted herein and for reasons of record, the *second nucleotide sequence* of binding motifs associated with the recited RNA splicing factors (*i.e.,* SR proteins; SR-related proteins; hnRNP proteins; U1 snRNP), including the splicing factors themselves, are well characterized and are known to a person of ordinary skill in the art. See, *e.g.*, Specification at page 11, last paragraph through page 13, line 2 (citing, *e.g.,* Graveley 2000; Kreicic & Swanson 1999; and McCullough & Berget, 2000 – each of record; see April 20, 2009 IDS, citation nos. 96, 111, and 125, respectively). Moreover, as previously noted, numerous splicing enhancer sequences are disclosed in the application including nucleotide sequences that are incorporated by reference such as, for example, Table 1 of Cartegni *et al.* 2002 (of record; see April 20, 2009 IDS, citation no. 32), which lists a number of RNA motifs that are recognized by human SR proteins. Specification at page 12, lines 3-6. Also, as previously noted, the person of ordinary skill in the art would readily be able to provide the *first nucleotide sequence* for targeting to a specific site on a target RNA sequence by complementary base pairing.

For the foregoing reasons, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims under 35 U.S.C. §112, 1st paragraph (Enablement) is Traversed

The Office rejected claims 23, 26, 28, 30-38, 40-43, and 61-78 as allegedly lacking enablement. Office Action at pages 6-11. Of these claims, only claims 23, 28, 30-32, 34-38, 41-43, 61, and 66-77 remain pending. In view of the foregoing amendment and the following remarks, the rejection is traversed.

According to the Office:

> Contrary to the Applicant's assertions, the references cited in support of the enablement rejection accurately the unpredictable in the art of gene therapy that remain today.
>
> The success of a particular oligonucleotide to provide in vivo affects does not necessarily provide assurance for clinical success for a different effector molecule (e.g., an inhibitory oligonucleotide) to successfully target a different target gene or to exert its effects predictably in an organism.
>
> One situation is not extrapolatable to another situation, especially where different effector molecules are used to target different genes of interest, or are involved in different biochemical mechanisms.

Office Action at page 5, lines 7-14 . The Office then quotes various specific passages from the citations (previously provided by Applicants in support of enablement), the Office stating that "they help illustrate the unpredictability of the field of gene therapy ...". Office Action at page 5, line 15 through page 8, line 2 (See, *e.g.,* Office assertion regarding Meyer *et al.* (2009) at pages 5-6; and regarding Marquis *et al.* (2007) at page 6).

A lack of enablement rejection is appropriate where the written description fails to teach those in the art to make and use the invention as broadly as claimed without *undue* experimentation. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). "The PTO cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description." *Id.* at 1357. "The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence." MPEP §2164.05.

While Applicants do not concede the merits of the rejection, they thank the Office for considering the references previously provided by Applicants. However, as noted herein and for reasons of record, Applicants maintain that *undue* experimentation is not required for the various embodiments of the claimed invention including *in vivo* embodiments.

Regarding the Office's comments on the Meyer *et al.* (2009) reference (Office Action at page 5, lines 21-22, bold type: "***reasons for this phenomenon***"), Applicants point out that the "*phenomenon*" under investigation, does NOT refer to splicing. Rather, it refers to the variation the authors observe in expression of their gene of interest. This has nothing to do with the principle of correcting splicing.

The Office's assessment of the Marquis *et al.* reference (Office Action at page 6) also is incorrect. One of ordinary skill in the art would expect careful selection and optimization of the target to be required. As with any technological application based on the use of oligonucleotides (*e.g.,* DNA sequencing, PCR, RNAi) a certain element of trial and error is normal, but this does not represent an *undue* burden. Indeed, the level of optimization required for any oligonucleotide-based technology, such as the present invention, is simply routine and expected.

It appears that the examiner's enablement rejection is based upon an alleged difficulty in delivering the *nucleic acid molecule* to the required sites in the body. This, however, was within the scope of the skilled person at the relevant date.

For example, as Applicants previously pointed out, one of ordinary skill in the art could readily design a vector, such as a viral vector (*e.g.,* Claims 71-76) to express and deliver the *nucleic acid molecule*. This could readily be used therapeutically, regardless of whether or not it is ideal. Meyer *et al* (2009), in fact, designed a viral expression system although they used it as a transgene in the published experiments. Thus, the skilled artisan could use this system to produce viral expression vectors and use them therapeutically. All of the steps are known in the art.

Although Applicants believe that they have provided sufficient evidence to support enablement of the claimed invention including *in vivo* embodiments, as additional evidence that the invention was sufficiently enabled at the time of filing, Applicants submit herewith five further scientific publications to support their position. Three of these documents report direct delivery of oligonucleotides into mice, and two of them report the use of oligonucleotides to alter

splicing in cells in culture (which for thalassemia is also a potential treatment). One of the documents, namely Zhang *et al.*, Nature Biotechnology, 18:862-867 (2000) (submitted herewith as exhibit), demonstrates a conventional use of antisense oligonucleotides to reduce gene expression when administered to mice, which is evidence of the enablement of systemic oligonucleotide delivery having a biological and therapeutic effect in the relevant cells *in vivo*. The other four documents show a direct effect of the administered antisense oligonucleotides to suppress the use of splice sites *in vivo* and *in vitro*. These documents are evidence of the enablement of *in vitro* and *in vivo* systemic oligonucleotide delivery having a direct biological effect at the site of splicing, which is the site of action of the oligonucleotides administered according to the method of the present invention. These five publications additionally evidence that direct delivery of oligonucleotides into organisms as a therapy was enabled at the time of filing.

For example, Lacerra *et al.*, PNAS, 97:9591–9596 (2000) (submitted herewith as exhibit) corrected the beta-globin splice mutation in mononuclear cells from thalassemia patients in culture using oligonucleotides antisense to the aberrant splice site. Lacerra *et al.* detected a restoration of correct splicing, leading to restoration of hemoglobin synthesis in the cells.

Suwanmanee *et al.*, Mol. Pharmacol., 62:545–553 (2002) (submitted herewith as exhibit) corrected the beta-globin splice mutation in erythroid precursor cells from thalassemia patients in culture using oligonucleotides antisense to the aberrant splice site. The authors found that the antisense morpholino oligonucleotide was able to penetrate the erythroid precursor cell membrane barrier and translocate to the nucleus, suggesting that similar results should be possible *in vivo*. Suwanmanee *et al* obtained similar results with precursor erythroid cells from the bone marrow of a transgenic mouse model of thalassemia. The corrected cells were reinjected into mice intraorbitally, and expression of the corrected mRNA appeared about 4 hours after injection and persisted for 2 days.

Sazani *et al.* (2002) (submitted herewith as exhibit) systemically administered various oligonucleotides via ***intraperitoneal*** injection into a transgenic mouse model designed as a positive readout test for activity, delivery, and distribution of antisense oligomers. Sazani *et al.* showed that the sequence-specific ability of the oligomers to correct a splicing defect and thereby

upregulate gene expression, and concluded that this validates the use of systemically delivered oligonucleotides as potential therapeutics.

Lu *et al.* (2003) (of record; see April 20, 2009 IDS, citation no. 121) systemically administered various oligonucleotides via ***intramuscular*** injection into the *mdx* dystrophic mouse, a model of muscular dystrophy. The oligonucleotides were designed to circumvent the dystrophic mutation in exon 23 by skipping this exon, thereby restoring dystrohpin levels. Lu *et al.* found that a single intramuscular injection of the oligonucleotide 2OMeAO resulted in expression of dystrophin for more than three months. Lu *et al.* concluded that this shows the real feasibility of using this strategy for the clinical treatment of muscular dystrophy, as well as other diseases in which exon splicing might be used to obviate mutations.

In addition, Zhang *et al. supra* showed that that inhibition of Fas expression using an antisense oligonucleotide inhibitor reduced the severity of fulminant hepatitis in mice. In tissue culture, this oligonucleotide induced a reduction in Fas mRNA expression that was both concentration- and sequence-specific. ***Intraperitoneal*** dosing of Balb/c mice with this oligonucleotide reduced Fas mRNA and protein expressions in liver by 90%. Pretreatment with this oligonucleotide completely protected mice from fulminant hepatitis induced by agonistic Fas antibody, by a mechanism entirely consistent with an oligonucleotide antisense mechanism of action. Zhang *et al.* also showed that after a single ***subcutaneous*** injection of oligonucleotide reduced Fas mRNA expression down to 20% of control levels, and this remained reduced for about 10 days. Zhang *et al.* conclude that the antisense oligonucleotide targeting Fas exerted *in vivo* pharmacological activity in liver, and that such oligonucleotide inhibitors of Fas may be useful in the treatment of human liver disease.

Thus, at the filing date of the present application, the above-cited art demonstrated two independent models in which systemic administration of oligonucleotides corrected a splicing defect *in vivo*, and a further model in which systemic administration of oligonucleotides had a therapeutic effect *in vivo*. Such methodologies are applicable to the present invention.

Thus, for example, Sazani *et al.* demonstrate modulation of splicing by antisense blocking oligonucleotides in heart, kidney, liver, lung, skeletal muscle and intestinal smooth muscle. One of ordinary skill in the art knows that the vascular system itself is accessible. And, a variety of modes of administration are known in the art including intrathecal injection (*e.g.*,

lumbar puncture) into the CNS. Moreover, delivery *via* viral vectors, especially vectors that express oligonucleotides as a small RNA, was already known and considered an option. Thus, the evidence shows that delivering the oligonucleotide to the required sites in the body in order to target a splicing defect was certainly within the skill and abilities of the person of ordinary skill in the art at the time of filing.

Also, more recently, *in vivo* results directly supporting the present invention have been published. For example, Baughan *et al.*, HMG Advance Access published February 19, 2009, Pages 1-48, Published by Oxford University Press (submitted herewith as exhibit) have shown that a bifunctional RNA, as defined in the present claims, binds SMN exon 7 and modulates SMN2 splicing. The bifunctional RNAs effectively increased SMN in human primary SMA fibroblasts. Lead candidates were synthesized as 2'-O-methyl RNAs and were ***directly injected in the central nervous system*** of SMA mice. Single-RNA injections were able to illicit a robust induction of SMN protein in the brain and throughout the spinal column of neonatal SMA mice. In a severe model of SMA, mean life span was extended following the delivery of bifunctional RNAs. Baughan *et al.* conclude that this technology has direct implications for the development of an SMA therapy, but also lends itself to a multitude of diseases caused by aberrant pre-mRNA splicing.

For the foregoing reasons, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims under 35 U.S.C. §103(a) is Traversed or Rendered Moot

The Office rejected claims 23, 26, 28, 30-38, 40-43, 61-69, and 71-78 as allegedly obvious over Mitchell et al (US 2003/0077754) ("Mitchell I") and Mitchell et al (US 2004/0126774) ("Mitchell II"), and Hofmann et al. (Proc. Natl. Acad. Sci., Vol. 97, No. 17, pages 9618-9623, 2000) ("Hofmann"), and further in view of Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45476-45483, 2001) ("Lim"), and Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999) ("Lorson"), the combination further in view of Dunckley et al (Human Molec. Genetics, Vol. 5, No. 1, pages 1083-1090, 1995) (Dunckley). Office Action at pages 8-12. Of these claims, only claims 23, 28, 30-32, 34-38, 41-43, 61, 66-69, and 71-77 remain

pending. In view of the foregoing amendment and the following remarks, the rejection is traversed or rendered moot.

The Office states that:

> ... relying on the teachings of Hofmann, Mitchell [I] and Mitchell [II], whereby administration of recombinant Htra2-Beta 1, or administration of pre-trans-splicing molecules designed to interact with the well known target precursor messenger RNA molecule of SMN would reasonably be expected to lead to trans-splicing to correct the mutated splice site in appropriate target cells in vitro.

Office Action at page 11, last line through page 12, line 4; emphasis added.

> One of ordinary skill in the art would have been motivated to correct this genetic defect because ... the means of generating pre-trans-splicing molecules to trans-splice the target pre-mRNA were also well known in the art to provide gene therapy approaches for correcting splicing disorders for known mutations.

Office Action at page 12, lines 5-9. Moreover, the additional secondary references relied-on by the Office, namely Lim, Lorson, and Dunckley, appear to be set forth as allegedly providing only various elements of further dependent claims.

The burden is on the Examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. Obviousness or nonobviousness of the claimed subject matter is determined against this background. *Id.*

Firstly, Applicants in no way acquiesce with respect to this rejection as applied to the previously pending claims. Nonetheless, in order to advance prosecution, sole independent claim 23 is amended herein to include the recitations "whereby the first specific binding pair and the second specific binding pair form to recruit the RNA splicing factor to an RNA splicing site on the target RNA species to effect RNA splicing of the target RNA at said RNA splicing site of the target RNA" and "wherein the RNA splicing factor is selected from the group consisting of SR proteins, SR-related proteins, hnRNP proteins, and U1 snRNP."

Mitchell I/Mitchell II

Firstly, Applicants respectfully point out that, as taught by the instant specification, an *enhancer sequence* can effect splicing in *trans* (*i.e.*, the *enhancer* is *acting* in *trans*). One of ordinary skill in the art knows that this is distinguishable from the "*trans splicing*" disclosed by Mitchell I and Mitchell II whereby a portion of one molecule (*e.g.*, an oligo X) is spliced to a different molecule (*e.g.*, a molecule Y).

Thus, as previously noted, the methods of Mitchell I and Mitchell II relate to *trans-splicing* a synthetic exogenous molecule (*i.e.*, the PTM) to a natural molecule (*i.e.*, the per-mRNA): "*a portion of the PTM [i.e., exogenous nucleic acid] is spliced to the natural pre-mRNA ...*". See, *e.g.*, Mitchell I Title and at page 2, paragraph [0013], lines 10-14; Mitchell II Title and at page 2, paragraph [0017], lines 10-14. In view of any fair reading of Applicants' specification and claims reciting "*to effect RNA splicing of the target RNA at said RNA splicing site of the target RNA, wherein exogenous nucleic acid is not incorporated into the target RNA species*," it must be recognized that the methods of Mitchell I and Mitchell II are antithetical to the methods of the claimed invention.

Accordingly, it is not understood how any teachings of Mitchell I and Mitchell II could contribute to any asserted expectation of success. Mitchell I and Mitchell II's "*trans splicing*" of a synthetic exogenous molecule to another molecule is simply not comparable to the claimed invention of the present application in any manner relevant to expection of success. The Applicant believes that this is fully evident from the teaching and discussion in the specification itself.

Hofmann

The method of Hofman, as it relates to splicing, is cotransfection of expression vectors encoding individual recombinant splicing factors with synthetic minigenes to effect splicing of the synthetic minigenes: "*splicing assays ... in cells, in which increasing amounts ... of expression vectors encoding the individual splicing factors were cotransfected with ... minigenes.*" See, *e.g.*, Hofmann at page 9619, Results, lines 11-15. In view of any fair reading of Applicants' specification and claims, it is not understood how any teaching of Hofman could contribute to any asserted expectation of success. Hofman's co-transfection of splicing factors and minigenes is simply not comparable to the claimed invention of the present application in any manner relevant to expection of success.

The Applicant believes that this is fully evident from the teaching and discussion in the specification itself.

Lim

As it relates to splicing, Lim teaches that an oligonucleotide can block one splice site and thereby divert splicing to another: "[Antisense oligonucleotides] directed toward the 3' splice site of exon 8 were shown to alter SMN2 splicing in favor of exon 7 inclusion." See, *e.g.*, Lim at page 45476, Abstract, lines 16-20; and at page 45477, left col., last line. Lim's antisense oligonucleotides are thus conventional blocking oligonucleotides that can not be characterized as capable of being within 100 nucleotides of conventional splicing signals because they must anneal right at those signals so as to block access by splicing factors.

In view of any fair reading of Applicants' specification and claims, it is not understood how any teaching of Lim could contribute to any asserted expectation of success. Lim's use of antisense oligonucleotides to block one splice site in order to divert splicing to another is simply not comparable to the claimed invention of the present application in any manner relevant to expection of success. The Applicant believes that this is fully evident from the teaching and discussion in the specification itself.

Lorson

As it relates to splicing, Lorson analyzes transcripts to determine the nucleotide(s) that differ between SMN1 and SMN2 that effect alternative splicing of exon 7. See, *e.g.*, Lorson at page 6307, Abstract, lines 10-13. In view of any fair reading of Applicants' specification and claims, it is not understood how any teaching of Lorson could contribute to any asserted expectation of success. Lorson's analysis of transcripts is simply not comparable to the claimed invention of the present application in any manner relevant to expection of success. The Applicant believes that this is fully evident from the teaching and discussion in the specification itself.

Dunckley

Dunckley's disclosure involves the use of an antisense oligonucleotide to induce exon skipping as applied to the dystrophin gene. In view of any fair reading of Applicants' specification and claims, it is not understood how any teaching of Dunckley could

contribute to any asserted expectation of success. Dunckley's use of antisense oligonucleotides in order to effect exon skipping is simply not comparable to the claimed invention of the application in any manner relevant to expection of success. The Applicant believes that this is fully evident from the teaching and discussion in the specification itself.

The additional secondary references relied-on by the Office, namely Lim, Lorson, and Dunckley, are not set forth as curing the noted deficiencies of Mitchell I, Mitchell II, and Hofmann as discussed above and for reasons of record. It is believed that none of the secondary references cure the noted deficiencies of Mitchell I, Mitchell II, and Hofmann as noted herein. There is simply nothing in any of the cited references, when considered alone or in combination, that teaches or suggests that an activating protein (splicing factor) can be recruited by an oligonucleotide to a specific target site on a separate RNA molecule to enhance splicing. Rather, when combining the teachings of the cited references, when considered in each of the possible ways identified in the Examination Guidelines, one would at best only arrive at variations of the *trans-splicing* method of Mitchell I and Mitchell II.

For at least the foregoing reasons, no combination of Mitchell I, Mitchell II, Hofmann, Lim, Lorson, and Dunckley would have rendered Applicants' invention as presently claimed obvious to one of ordinary skill in the art. Accordingly, a *prima facie* case of obviousness has not been established, therefore, the rejection must be withdrawn.

Morever, even if, solely for the sake of argument, Applicants assume that a *prima facie* case of obviousness has been established, the *prima facie* case is rebutted by important secondary indicia of nonobviousness for reasons of record.

Accordingly, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

CONCLUSION

Applicants believe these Amendments and Remarks place the claims in condition for allowance/issuance and such action is respectfully requested. If issues may be resolved through Examiner's Amendment, or clarified in any manner, a call to the undersigned attorney is respectfully requested.

Respectfully submitted,

Date: January 22, 2010

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